REMARKS

1. Formal Matters

a. Status of the Claims

Claims 69-88 are pending in this application. Claims 69-72 are amended; claims 89-96 are new; and claims 73-88 are hereby canceled without prejudice to pursuing the canceled subject matter in a continuing application. Upon entry of these amendments, claims 69-72 and 89-96 are pending and under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application.

b. Amendments to the Claims

Claim 69 is amended to recite an isolated nucleic acid consisting of X nucleotides, wherein X=19 to 140, which is a rephrasing of the limitation "consisting of 19 to 140 nucleotides" of previously-presented claim 69. Part (a) of claim 69 is amended to recite "Y consecutive nucleotides of SEQ ID NO: 142700," wherein X≥19 and X≥Y, which is a rephrasing of the limitation "at least 19 consecutive nucleotides" of previously-presented claim 69. The foregoing amendments to the preamble and part (a) of claim 69 do not change the scope of the claim. Part (c) of claim 69 has been stricken. The foregoing amendments are being made for purposes of clarifying the claimed subject matter and not for reasons of patentability.

Claim 70 is amended to recite the nucleic acid of claim 69, wherein the Y nucleotides are of SEQ ID NO: 140670 or 140732, which is a rephrasing of the limitation "the at least 19 nucleotides is of a sequence selected from the group consisting of SEQ ID NOS: 140670 and 140732" of previously-presented claim 70. Applicant respectfully submits that the amendment of claim 70 maintains antecedent basis with amended claim 69 and does not change the scope of the claim.

Claim 71 is amended to recite the nucleic acid of claim 69, wherein X=19 to 24, which is a rephrasing of the limitation "the nucleic acid consists of 19 to 24 nucleotides" of previously-presented claim 71. Applicant again submits that the amendment of claim 71 maintains antecedent basis with amended claim 69 and does not change the scope of the claim.

Claim 72 is amended to recite the nucleic acid of claim 69, wherein X=Y. Amended claim 72 maintains antecedent basis and draws support from claim 69 in a similar manner as described above.

New claim 89 recites an isolated nucleic acid consisting of X nucleotides, wherein X=19 to 140, support for which can be found at paragraphs 0042, 0045, and 0046 of the specification as originally filed. For example, paragraph 0042 recites "An Oligonucleotide is defined as a nucleic acid comprising 2-139

nucleotides, or preferably 16-120 nucleotides." Paragraph 0045 describes, "an oligonucleotide having a nucleotide sequence that is 50-140 nucleotides in length…" Paragraph 0046 describes, "an oligonucleotide which is about 19 to about 24 nucleotides in length." These four disclosed ranges of length overlap for the claimed nucleic acids. Accordingly, the specification, as filed, discloses a nucleic acid 19 to 140 nucleotides in length.

Part (a) of new claim 89 recites Y consecutive nucleotides of SEQ ID NO: 2 or 9, wherein Y≥19 and X≥Y, support for which can be found at the Sequence Listing as originally filed and as described above for claim 69. Part (c) of new claim 89 recites an RNA equivalent of (a), support for which can be found at paragraph 0040 of the specification as originally filed. Paragraph 0040 recites, "A Nucleic acid is defined as a ribonucleic acid (RNA) molecule or a deoxyribonucleic acid (DNA) molecule…"

Part (c) of new claim 89 recites a sequence at least 68.2% identical to (a) or (b), support for which can be found at Table 1, lines 8 and 484, Table 2, lines 19180-19280 and 25271-25367, and Table 7, lines 188035-188829 and 251096-253839 of the application as originally filed. Table 1 discloses that the miRNAs GAM3298 (line 8 of Table 1) and GAM2608 (line 484 of Table 1) have the sequences as set forth in SEQ ID NOs: 2 and 9, respectively, as follows:

GAM SEQ-ID	GAM NAME	GAM RNA SEQUENCE	GAM POS
2	GAM3298	AAAGTGCTCATAGTGCAGGTAG	A
9	GAM2608	TAAGGTGCATCTAGTGCAGTTA	A

Table 2 discloses that GAM3298 and GAM2608 are encoded by the precursor hairpins with the sequences as set forth in SEQ ID NOs: 140732 and 140670, respectively, as follows:

GAM NAME	PRECUR SEQ-ID	PRECURSOR SEQUENCE	GAM DESCRIPTION
GAM3298	140732	TTGGGTCCTA GTAGTACCAA AGTGCTCATA GTGCAGGTAG	Fig. 8 further provides a conceptual description of another novel bioinformatically detected oligonucleotides of the present invention, referred to here as Genomic Address Messenger 3298 (GAM3298) oligonucleotides modulates expression of respective target genes whose function and utility is known in the art.
		TTTTGGCATG ACTCTACTGT AGTATGGGCA	GAM3298 is a novel bioinformatically detectable regulatory, non protein coding, micro RNA (miRNA)-like oligonucleotide. The method by which GAM3298 was detected is described with additional reference to Figs. 9-15.
		CTTCCAGTAC TCTTGGATAA	GAM PRECURSOR DNA is encoded by the human genome. GAM TARGET GENE is a humen gene encoded by the human genome.
		CAA	GAM3298 precursor DNA, herein designated GAM PRECURSOR DNA, encodes a GAM3298 precursor RNA, herein designated GAM PRECURSOR RNA. Similar to other miRNA genes GAM3298 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of GAM3298 precursor RNA is designated SEQ ID:140732, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:140732 is located from position 131248823 to position 131248915 relative to chromosome chrX on the `-` strand (chr is an abbreviation for chromosome).
GAM2608	140670	CTTTTGAGCT GCTTCTTATA ATGTGTCTCT TGTGTTAAGG	Fig. 8 further provides a conceptual description of another novel bioinformatically detected oligonucleotides of the present invention, referred to here as Genomic Address Messenger 2608 (GAM2608) oligonucleotides modulates expression of respective target genes whose function and utility is known in the art.
		TGCATCTAGT GCAGTTAGTG AAGCAGCTTA	GAM2608 is a novel bioinformatically detectable regulatory, non protein coding, micro RNA (miRNA)-like oligonucleotide. The method by which GAM2608 was detected is described with additional reference to Figs. 9-15.
		GAATCTACTG CCCTAAATGC	GAM PRECURSOR DNA is encoded by the human genome. GAM TARGET GENE is a humen gene encoded by the human genome.
		CCCTTCTGGC ACAGGCTGCC TAATATACAG CATTTTAAAA G	GAM2608 precursor DNA, herein designated GAM PRECURSOR DNA, encodes a GAM2608 precursor RNA, herein designated GAM PRECURSOR RNA. Similar to other miRNA genes GAM2608 precursor RNA does not encode a protein. A nucleotide sequence identical or highly similar to the nucleotide sequence of GAM2608 precursor RNA is designated SEQ ID:140670, and is provided hereinbelow with reference to the sequence listing part. Nucleotide sequence SEQ ID:140670 is located from position 131249037 to position 131249167 relative to chromosome chrX on the `-` strand (chr is an abbreviation for chromosome).

Table 7, lines 188035-188829 disclose that the miRNA GAM3298 (SEQ ID NO: 2) is capable of binding to sites within 326 target gene mRNAs (See Exhibit A, submitted herewith). Table 7 further discloses that 15 out of 22 nucleotides (68.2%) of GAM3298 are sufficient for binding target mRNAs. For example, 68.2% of the residues of SEQ ID NO: 2 are capable of targeting mRNAs of the genes HIP1 and ADCY1, as follows:

GAM NAME SEQUENCE	GAM RNA	TARGET REF-ID	TARGET	UTR	TARGET BS-SEQ (UPPER:GAM;LOWER:TARGET)	BINDING-SITE DRAW (UPPER:GAM;LOWER:TARGET)	GAM POS
GAM3298	AAAGTGCTCAT AGTGCAGGTAG	HIP1	NM_005338.3	3	ACGCCTGTAATCC CAGCACTTT	CATAG AG AAAGTGCT TGCAGGT TTTCACGA ATGTCCG CCCTA CA	A
GAM3298	AAAGTGCTCAT AGTGCAGGTAG	ADCY1	NM_021116.1	3	TGTTTGCACTATA CTTT	GCTC GG AAAGT ATAGTGCA TA TTTCA TATCACGT GT ---- TT	A

Table 7 also discloses that the mRNA GAM2608 (SEQ ID NO: 9) is capable of binding to sites within 117 target gene mRNAs (See Exhibit B, submitted herewith). Table 7 further discloses that 15 out of 22 nucleotides (68.2%) of GAM2608 are sufficient for binding target gene mRNAs. For example, 68.2% of the residues of SEQ ID NO: 9 are capable of targeting mRNAs of the genes CALCB and EGR4, as follows:

```
GAM2608   TAAGGTGCATC CALCB   NM_000728.2  3  TAATTGCCCCTGC T        TCTAGT                A
          TAGTGCAGTTA                          ACCTTT         AAGGTGCA      GCAGTTA
                                                              TTCCACGT      CGTTAAT
                                                             T        CCC---
GAM2608   TAAGGTGCATC EGR4    NM_001965.1  3  TAACTGCACACGC T      CATCTA--                A
          TAGTGCAGTTA                          CCCACGCCTTC    AAGGTG        GTGCAGTTA
                                                              TTCCGC        CACGTCAAT
                                                             C      ACCCCGCA
```

Part (d) of new claim 89 recites the complement of any one of (a)-(c), support for which can be found at paragraph 0040 of the specification as originally filed. Paragraph 0040 recites, "A nucleic acid is defined as … complementary deoxyribonucleic acid (cDNA)…"

New claim 90 recites the nucleic acid of claim 89, wherein (c) is a sequence at least 81.9% identical to (a) or (b), support for which can be found at Table 7 of the application as originally filed. Table 7 discloses that 18 out of 22 nucleotides (81.9%) of the miRNA GAM3298 (SEQ ID NO: 2) are sufficient for binding target gene mRNAs. For example, 81.9% of the residues of SEQ ID NO: 2 are capable of targeting mRNAs of the genes ABCC3 and ADSL, as follows:

```
GAM3298   AAAGTGCTCAT ABCC3   NM_020037.1  3  TACCTGCACTGTC AAA    -----   ---             A
          AGTGCAGGTAG                          CTGACCATCGCAC    GTGC     TCA   TAGTGCAGGTA
                                                              CACG     AGT   GTCACGTCCAT
                                                             ---    CTACC   CCT

GAM3298   AAAGTGCTCAT ADSL    NM_000026.1  3  TTACCTTAAATTA         CA--    GC-             A
          AGTGCAGGTAG                          GTACAGCACTTT  AAAGTGCT    TAGT   AGGTAG
                                                             TTTCACGA    ATTA   TCCATT
                                                                     CATG    AAT
```

Table 7 also discloses that 18 out of 22 nucleotides (81.9%) of the miRNA GAM2608 (SEQ ID NO: 9) are sufficient for binding target gene mRNAs. For example, 81.9% of the residues of SEQ ID NO: 9 are capable of targeting mRNAs of the genes ABCC3 and CASP3, as follows:

```
GAM2608   TAAGGTGCATC ABCC3   NM_020038.1  3  TAGCAAACACTGG         AT      CA-             A
          TAGTGCAGTTA                          GGGCACCTTA    TAAGGTGC  CTAGTG   GTTA
                                                             ATTCCACG  GGTCAC   CGAT
                                                                     GG      AAA

GAM2608   TAAGGTGCATC CASP3   NM_032991.1  3  TAACTGCATTTTA TA     CA    --              A
          TAGTGCAGTTA                          GACCATTTAT      AGGTG  TCTA  GTGCAGTTA
                                                              TTTAC  AGAT  TACGTCAAT
                                                             TA     C-    TT
```

New claim 91 recites the nucleic acid of claim 89, wherein (c) is a sequence at least 91.0% identical to (a) or (b), support for which can be found at Table 7 of the application as originally filed. Table 7 discloses that 20 out of 22 nucleotides (91.0%) of the miRNA GAM3298 (SEQ ID NO: 2) are sufficient for binding target gene mRNAs. For example, 91.0% of the residues of SEQ ID NO: 2 are capable of targeting mRNAs of the genes ASTN and MECP2, as follows:

```
GAM3298   AAAGTGCTCAT ASTN    XM_045113.2  3  ATGCCAGGCGCTG         --   -     A-    G      A
          AGTGCAGGTAG                        ATGTAAGCACTTT AAAGTGCT  CAT AGTGC  GGTA
                                                           TTTCACGA  GTA TCGCG  CCGT
                                                                   AT   G     GA    A

GAM3298   AAAGTGCTCAT MECP2   NM_004992.2  3  TTATTTGCACTAT A   T     -                    A
          AGTGCAGGTAG                        TGAGTCTTC      AAG GCTCA TAGTGCAGGTAG
                                                            TTC TGAGT ATCACGTTTATT
                                                           C   -     T
```

Table 7 also discloses that 20 out of 22 nucleotides (91.0%) of the miRNA GAM2608 (SEQ ID NO: 9) are sufficient for binding target gene mRNAs. For example, 91.0% of the residues of SEQ ID NO: 9 are capable of targeting mRNAs of the genes MAP4K5 and MMP26, as follows:

```
GAM2608   TAAGGTGCATC MAP4K5  NM_006575.2  3  AAACTGCACTATG        C   -          A         A
          TAGTGCAGTTA                        ATTTGCTTTA    TAAGGTG ATC TAGTGCAGTT
                                                           ATTTCGT TAG ATCACGTCAA
                                                                  T   T          A

GAM2608   TAAGGTGCATC MMP26   NM_021801.2  3  AACTGAAAGCACT      -   A        ----          A
          TAGTGCAGTTA                        AGAGCAGCCTTG  TAAGG TGC TCTAGTGC    AGTT
                                                           GTTCC ACG AGATCACG    TCAA
                                                                G   -        AAAG
```

New claim 92 recites the nucleic acid of claim 89, wherein X=19 to 24, support for which can be found as describe above for claim 89.

New claim 93 recites the nucleic acid of claim 89, wherein X=Y, antecedent basis and support for which can be found as described above for claim 89.

New claim 94 recites the nucleic acid of claim 90, wherein X=Y, antecedent basis and support for which can be found as described above for claim 90.

New claim 95 recites the nucleic acid of claim 91, wherein X=Y, antecedent basis and support for which can be found as described above for claim 91.

New claim 96 recites a vector comprising the nucleic acid of any one of claims 69-72 and 89-95, support for which can be found at paragraphs 0039-0041 of the specification as originally filed. Paragraph 0039 recites, "the invention provides several substantially pure nucleic acids (e.g., genomic DNA, cDNA or synthetic DNA) each comprising a novel GAM oligonucleotide, vectors comprising the DNAs…"

2. Patentability Remarks

a. Rejections under 35 U.S.C. § 112, 2nd paragraph, Indefiniteness

On page 3 of the Office Action, the Examiner rejects claims 69-86 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Claims 69 and 72

The Examiner asserts that the phrase "at least 92/131 in claims 69 and 72 is vague and unclear. Applicant respectfully submits neither amended claim 69 nor amended claim 72 recites this term, thereby rendering the rejection moot.

Claim 72

The Examiner also asserts that claim 72 does not further limit claim 69, because claim 69 already encompasses nucleic acids that consist of at least 19 consecutive nucleotides of SEQ ID NO: 142700. Applicant respectfully disagrees. Nevertheless, Applicant respectfully submits that amended claim 69 is related to an isolated nucleic acid **comprising** a sequence of SEQ ID NO: 142700, and amended claim 72 is related to an isolated nucleic acid **consisting** of a sequence of SEQ ID NO: 142700.

Claims 79 and 80

The Examiner further asserts that the term "at least 14/22 complementary" of claims 79 and 80 is vague and unclear. Applicant respectfully submits that claims 79 and 80 are canceled without prejudice, thereby rendering the rejection moot.

Claims 85 and 86

The Examiner also asserts that the term "a gene expression inhibition system" of claims 85 and 86 is vague and unclear. Applicant respectfully submits that claims 85 and 86 are canceled without prejudice, thereby rendering the rejection moot.

The Examiner also rejects claims 70, 71, 73-78, and 81-84 because they are dependent on claims that the Examiner has alleged are indefinite. Applicant respectfully submits that 70 and 71 are not indefinite as these claims depend from amended claim 69, which is not indefinite. As discussed above, claims 73-78 and 81-84 are canceled without prejudice. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 69-86 under 35 U.S.C. § 112, second paragraph.

b. Rejections under 35 U.S.C. § 112, 1st paragraph, Written Description-New Matter

On pages 3-5, the Examiner rejects claims 69-86 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement because the claims allegedly contain new matter. On page 5 of the Office Action, the Examiner rejects these claims in part because the Examiner asserts that Tables 4, 7, and 10 could not be located and cannot be used as support for the claims. The Examiner has asked Applicant to review the specification and identify the location of Tables 4, 7, and 10.

Applicant respectfully submits that Tables 4, 7, and 10 were filed with the application on January 29, 2004. Applicant submits that the Utility Patent Filing Acknowledgement Receipt (Exhibit C, submitted herewith) indicates that external tables "Table4.txt" and "Table10.txt" (marked with arrows) of 1219401 and 1716661 Bytes in size, respectively, were successfully submitted via EFS-Web on the filing date. Applicant further submits that the Artifact Sheet (Exhibit D, submitted herewith) indicates that three CDs containing unspecified or combined content were received in connection with the instant application, but not scanned. The Artifact Cover Sheet (Exhibit E, submitted herewith) indicates that on the filing date, a file "Table7.txt" (marked with an arrow) was not scanned into the Image File Wrapper, but may be accessed in PALM under the location serial number. Accordingly, Applicant respectfully submits that Tables 4, 7, and 10 were received by the Office with the application as filed. Applicant welcomes the Examiner to contact the undersigned to further discuss the Tables if necessary.

"At least 92/131," Claims 69 and 72

On page 4 of the Office Action, the Examiner asserts that the specification as originally filed does not provide written description support for the term "at least 92/131" of claims 69 and 72. As described above, this term is not recited in the amended claims, thereby rendering the rejection moot.

"At least 14/22 complementary," Claims 79 and 80

The Examiner also asserts that the specification as originally filed does not provide written description support for the term "at least 14/22 complementary" of claims 79 and 80. As described above, this term is not recited in the amended claims, thereby rendering the rejection moot.

19-140 nucleotides, Claim 69

The Examiner further asserts that the specification as originally filed does not provide written description support for the size limitation of 19-140 nucleotides of claim 69. Applicant respectfully disagrees. Applicant respectfully submits that the written description requirement is satisfied if the specification conveys with reasonable clarity to those skilled in the art that Applicant at the time of filing was in possession of the invention as now claimed. *See* M.P.E.P. 2163.I.B. Applicant also submits that added claim limitations may be supported in the specification through express, implicit, or inherent disclosure. *Id.* With respect to range limitations, Applicant submits that the analysis of a numerical range limitation must take into account which ranges one of skill in the art would considered inherently supported by the original disclosure. *See* M.P.E.P. 2163.05.III

As described above, paragraphs 0042, 0045, and 0046 describe overlapping length limitations of 16-120 (¶ 0042), 50-140 (¶ 0045), and 19-24 (¶ 0046) for the claimed nucleic acids. The claimed precursor hairpins of GAM3298 and GAM2608 as set forth in SEQ ID NOs: 140732 and 140670 are

specifically described in Table 2 as being 93 nucleotides and 131 nucleotides in length respectively. The claimed miRNAs GAM3298 and GAM2608 as set forth in SEQ ID NOs: 2 and 9 are specifically described in Table 1 (lines 8 and 484) as each being 22 nucleotides in length. Applicant submits that the length limitations described in paragraphs 0042, 0045, and 0046, and Tables 1 and 2 clearly imply to one of skill in the art that, at the time of filing, Applicant was in possession of nucleic acids ranging from 19 to 140 nucleotides in length. *See* M.P.E.P. 2163.05.III (a range of "25%-60%" and specific examples of "36%" and "50%" in the original specification are sufficient written description support for a new limitation "between 35% and 60%"). Accordingly, Applicant respectfully submits that the specification as filed provides written description support for a nucleic acid 19 to 140 nucleotides in length.

"RNA equivalent," Claims 69 and 72

The Examiner also asserts that the specification as filed does not provide written description support for the term "an RNA equivalent of (a)" of claims 69 and 72. Applicant respectfully disagrees. Applicant respectfully submits that the written description requirement is satisfied if the specification describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that Applicant had possession of the claimed subject matter. *See* M.P.E.P. 2163.I. Applicant submits that SEQ ID NOs: 142700, 140670, and 140732 are GR Precursor DNA sequences (see instant paragraph 0288). The specification furthers discloses these GR Precursor DNAs encodes a GR Precursor RNAs (*Id.*). Applicant submits that one of ordinary skill would immediately conclude Applicant was also in possession of an RNA equivalent of this sequence according to these teachings. Accordingly, Applicant submits that the limitation "an RNA equivalent of (a)" satisfies the written description requirement.

In view of the foregoing remarks and amendments, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 69-86 under 35 U.S.C. § 112, first paragraph for allegedly containing new matter.

c. Rejections under 35 U.S.C. § 112, 1st paragraph, Lack of Written Descriptive Support

On pages 5-7 of the Office Action, the Examiner rejects claims 69-86 under 35 U.S.C. § 112, first paragraph, for allegedly encompass sequences not been adequately described in the specification. Specifically, the Examiner asserts that claims 69 and 72 appear to encompass sequences that are at least 70% identical to SEQ ID NO: 142700. The Examiner further asserts that the claims thus encompass an extremely large genus of variant molecules of SEQ ID NO: 142700, but that no common element or attributes of the sequences are disclosed because the specification does not disclose a representative number of sequences. The Examiner concludes that only specifically identified SEQ ID NOs: 142700, 140670, 140732, 2, and 9 are described. Applicant notes that amended claims 69 and 72 do not recite the limitation "at least 92/131 identical to (a) or (b)," but rather relate specifically to sequences comprising

SEQ ID NO: 142700, 140670, and 140732, thereby rendering the rejection moot. Nevertheless, Applicant disagrees.

Applicant respectfully submits that the written description requirement is satisfied if the specification describes the claimed subject matter in sufficient detail that one of skill in the art can reasonably conclude that Applicant had possession of the claimed subject matter. *See* M.P.E.P. 2163.I. Applicant further submits that Applicant may show possession of the claimed subject matter by describing the claimed subject matter with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Id.* Applicant submits that Table 7 discloses a large number of target mRNAs to which GAM3298 and GAM2608 are capable of binding with less than 100% complementarity. Paragraph 0267 discloses that target gene binding sites can be "partially or fully complementary" to the miRNAs described in the application. Paragraphs 0280-0282 of the specification specifically indicate three classes of binding sites that are partially complementary to the miRNAs described in the application. Additionally, Table 7, lines 251096-253839 and 188035-188829 discloses miRNA-target mRNA binding site interaction diagrams indicating that the miRNAs GAM3298 (SEQ ID NO: 2) and GAM2608 (SEQ ID NO: 9) are capable of binding to sites in 326 and 117 target gene mRNAs, respectively, with less than 100% complementarity (See Exhibits A and B).

The miRNA-target mRNA binding site interactions shown in Table 7 indicate that 68.2% (15 out of 22 nucleotides), 81.9% (18 out of 22), and 91.0% (20 out of 22) of the residues of SEQ ID NOS: 2 and 9 are capable of binding numerous target genes (*i.e.*, 326 target gene mRNAs by SEQ ID NO: 2 and 117 target gene mRNAs by SEQ ID NO: 9). From these teachings, it is evident that variant nucleic acids that have the same number of conserved residues as shown in the miRNA-target mRNA diagrams in Table 7 (*i.e.*, sequences at least 68.2%, 81.9%, and 91.0% identical to SEQ ID NOS: 2 and 9) are capable of binding numerous target gene mRNAs and regulating their expression. Accordingly, the disclosed interaction between GAM 3298 and GAM2608 miRNAs and their respective target gene mRNAs in Table 7 sufficiently teaches a representative number of possible variants of SEQ ID NOs: 2 and 9 (GAM3298 and GAM2608, respectively) that can regulate various target genes. Thus, Applicant respectfully submits that one of ordinary skill in the art would clearly understand from the application as filed that Applicant was in possession of variants of the claimed sequences that are at least 68.2%, 81.9% and 91.0% identical to the claimed sequences. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

d. Rejections under 35 U.S.C. §§ 101 and 112, 1st paragraph

On pages 7-13 of the Office Action, the Examiner rejects claims 69-86 under 35 U.S.C. § 101 and 35 U.S.C. §112, first paragraph, because the claimed subject matter allegedly is not supported by either a specific and substantial asserted utility, or alternatively, a well established utility. Applicant respectfully disagrees. Applicant respectfully submits that in order to satisfy the utility requirement under the Revised Interim Utility Guidelines, a specific and substantial utility must either (i) be cited in the specification, or (ii) be recognized as well established in the art, and the utility must be credible.

(1) Specific Utility

A specific utility is defined in the Revised Interim Utility Guidelines Training Materials ("RIUGTM") as a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" is not considered to be specific in the absence of a disclosure of a specific DNA target. *See* RIUGTM at page 5.

On page 12 of the Office Action, the Examiner asserts that neither the instant specification nor the prior art presents any evidence that the claimed nucleic acids have any specific biological function. Applicant respectfully disagrees. Applicant respectfully submits that the instant application identifies specific genes of interest that the claimed nucleic acids may be used to regulate expression. At Table 10, lines 267-330 of the specification, it is asserted that the disclosed GR7405 precursor DNA (with the nucleotide sequence as set forth in SEQ ID NO: 142700) encodes the miRNAs GAM3298 and GAM2608, which may be used to target and modulate expression of particular mRNA transcripts.[1] Furthermore, Table 10, lines 267-330 disclose that the claimed nucleic acids, which are related to the miRNA encoded by the GAM3298 gene, which may be used to modulate expression of particular target

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[1] The precursor DNA GR7405 encodes GAM3298 and GAM2608. GR7405 is described in Table 10, lines 267-330 of the application as filed, as follows:

> GR7405 precursor DNA encodes GR7405 precursor RNA, herein designated GR PRECURSOR RNA, an RNA molecule, typically several hundred to several thousand nucleotides long. Nucleotide sequence of GR7405 is located from position 131248823 to position 131249168 relative to chromosome chrX on the `-` strand (chr is an abbreviation for chromosome)…

SEQ ID NO: 142700 (GR7405) corresponds to the sequence of human chromosome X on the minus strand from position 131248823 to position 131249168. Table 10 also discloses that, "GR7405 folded precursor RNA, herein designated GR FOLDED PRECURSOR RNA, is naturally processed by cellular enzymatic activity into at least 2 separate GAM precursor RNAs, GAM2608 precursor RNA and GAM3298 precursor RNA…" Table 10 further discloses that, "The above mentioned GAM folded precursor RNAs are diced by DICER COMPLEX of Fig.8, yielding respective short RNA segments of about 22 nucleotides in length, GAM2608 RNA and GAM3298 RNA…" Accordingly, SEQ ID NO: 142700 (GR7405) is processed to produce the miRNAs GAM3298 and GAM2608.

mRNA transcripts such as those shown in Table 7.[2] Table 7 discloses that 326 target genes, such as Huntingtin Interacting Protein 1 (HIP1), are specific genes that may be targeted by the miRNA related to the claimed GAM3298 nucleic acid (SEQ ID NO: 2).[3]

Table 10, lines 267-330 also discloses that the claimed nucleic acids, which are related to the miRNA encoded by the GAM2608 gene, may be used to modulate expression of particular target mRNA transcripts such as those shown in Table 7.[4] Table 7 discloses that 117 target genes, such as Beta-Site APP-Cleaving Enzyme (BACE), are specific genes that may be targeted by the miRNA related to the claimed GAM2608 nucleic acid (SEQ ID NO: 9).[5] Accordingly, Applicant respectfully submits that the specification provides a specific utility for the claimed nucleic acids, namely binding and inhibiting numerous specific target genes.

(2) Substantial Utility

A substantial utility is defined in the RIUGTM as a utility that defines a "real world" use, which is contrast to the need to carry out further research to identify or confirm a "real world" context. As discussed above, the claimed GR7405 (SEQ ID NO: 142700) encodes nucleic acids (GAM3298 and

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[2] Table 10, lines 267-330 of the application discloses that:

> GAM3298 RNA, herein schematically represented by GAM1 RNA through GAM3 RNA, binds complementarily to a target binding site located in an untranslated region of GAM3298 target RNA, herein schematically represented by GAM1 TARGET RNA through GAM3 TARGET RNA, which target binding site corresponds to a target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 8, thereby inhibiting translation of GAM3298 target RNA into GAM3298 target protein, herein schematically represented by GAM1 TARGET PROTEIN through GAM3 TARGET PROTEIN, both of Fig. 8. (emphasis added)

[3] See Tables 7, lines 251096-253839 as provided in Appendix A for a description of all 326 target genes of the miRNA related to the claimed GAM3298 nucleic acid. For a description of the HIP1 specific target gene of miRNA related to GAM3298, see lines 25202-252061 of Table 7 and lines 784679-790022 of Table 8.

[4]Table 10, lines 267-330 discloses that:

> GAM2608 RNA, herein schematically represented by GAM1 RNA through GAM3 RNA, binds complementarily to a target binding site located in an untranslated region of GAM2608 target RNA, herein schematically represented by GAM1 TARGET RNA through GAM3 TARGET RNA, which target binding site corresponds to a target binding site such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig. 8, thereby inhibiting translation of GAM2608 target RNA into GAM2608 target protein, herein schematically represented by GAM1 TARGET PROTEIN through GAM3 TARGET PROTEIN, both of Fig 8. (emphasis added)

[5] See Table 7, lines 188035-188829 as provided Appendix B for a description of all 117 target genes of the miRNA related to the claimed GAM2608 nucleic acid. For a description of the BACE specific target gene of miRNA related to GAM2608, see lines 188060-188070 of Table 7 and lines 660648-662794 of Table 8.

GAM2608 miRNAs) that may be used to regulate expression of proteins encoded by hundreds of target mRNAs as listed in Table 7 (See Appendix A and Appendix B). Specifically, the encoded GAM3298 miRNA as set forth in SEQ ID NO: 2 may be used to regulate expression of proteins encoded by 326 target genes. The encoded GAM2608 miRNA as set forth in SEQ ID NO: 9 may be used to regulate expression of proteins encoded by 117 target genes. These target genes are associated with particular disease states or essential biological functions. For example, the encoded GAM3298 miRNA as set forth in SEQ ID NO: 2 may be used to regulate expression of a protein encoded by HIP1 mRNA. Table 8, lines 784679-790022 discloses that the gene HIP1 is known to be associated with Huntington disease:

> Huntingtin Interacting Protein 1 (HIP1, Accession NM_005338.3) is another GAM3298 target gene.... Another function of GAM3298 is therefore inhibition of HIP1, a GAM3298 target gene which is a membrane protein and interacts with huntington and therefore is associated with Huntington disease. Accordingly, utilities of GAM3298 include diagnosis, prevention and treatment of Huntington disease, and of other diseases and clinical conditions associated with HIP1.

The encoded GAM2608 miRNA as set forth in SEQ ID NO: 9 may be used to regulate expression of a protein encoded by BACE mRNA. Table 8, lines 660648-662794 discloses that the gene BACE is known to be associated with Alzheimer's disease:

> Beta- site APP- cleaving Enzyme (BACE, Accession NM_138973.1) is another GAM2608 target gene.... Another function of GAM2608 is therefore inhibition of BACE, a GAM2608 target gene which is responsible for the proteolytic processing of the amyloid precursor protein and therefore is associated with Alzheimer. Accordingly, utilities of GAM2608 include diagnosis, prevention and treatment of Alzheimer, and of other diseases and clinical conditions associated with BACE.

One of ordinary skill in the art would recognize that the claimed polynucleotides may be used to regulate expression of proteins of interest such as HIP1 and BACE. Accordingly, Applicant respectfully submits that the specification provides a substantial utility for the claimed nucleic acids.

(3) Credible Utility

According to the RIUGTM, an asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. *See* RIUGTM at page 5.

On page 10 of the Office Action, the Examiner asserts that the uses for the instant claimed nucleic acids in regulating gene expression are inherent to almost any miRNA. Applicant respectfully disagrees.

Applicant respectfully submits that the Examiner has not considered the asserted utility as discussed above for using the claimed nucleic acids for modulating expression of **specific mRNA targets**. Whether or not the claimed nucleic acids actually exist in a biological system, and could be used as probes, translation repressors of target gene mRNAs, or treating diseases is irrelevant. The proper inquiry is instead whether one of ordinary skill in the art would believe that the claimed nucleic acids **may be** used to modulate expression of **the specific mRNA targets**.

Paragraph 0265 of the specification discloses that the mRNA targets of the claimed nucleic acids were identified as being consistent with the free energy and spatial structure of target binding sites of known miRNAs. The method as described in paragraph 0265 for identifying target binding sites of miRNAs is based upon studies at the time of filing demonstrating that miRNAs bind to sites in target mRNAs as disclosed in references such as Wightman *et al.* (1993), Reinhart *et al.* (2000), Slack *et al.* (2000), Lau *et al.* (2001), Lagos-Quintana *et al.* (2001), and Moss *et al.* (1997), which are all cited in the Information Disclosure Statement filed October 6, 2006 under reference numbers 30, 260, 300, 780, 790, and 100, respectively. In view of the asserted utilities being consistent with the general understanding of miRNAs and their target binding sites at the time of filing, Applicant respectfully submits that one of ordinary skill in the art would believe that each claimed nucleic acid would bind its respective target binding sites.

In view of the foregoing remarks and lack of showing that Applicant's assertion of utility is seriously flawed or logically inconsistent, the Applicant respectfully submits that a credible utility is asserted for the claimed nucleic acids. Also, the Applicant submits one of skill would be able to use the claimed invention due to its asserted utility. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 69-86 under 35 U.S.C. §§ 101 and 112, first paragraph.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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Dated: June 11, 2007

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